REMARKS

Claims 17, 20-22, 24-27, 29-31 and 33 are pending in the present application and are rejected. Claim 17 is herein amended. Claims 1-16 and 34-42 are herein cancelled without prejudice.

Preliminary Comments

Applicants note that the Office Action states that documents JP 2002-333446 and JP 4-501605 were not considered because no English language translation was provided. However, as noted on the IDS, these references correspond to English-language documents. As such, Applicants respectfully submit that the concise statement of relevance is satisfied by the correspondence to the English-language references. Thus, Applicants respectfully request that these references be initialed.

Applicants' Response to Claim Rejections under 35 U.S.C. §112

Claims 17 and 20 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action indicates that the singular recitation of "said double-stranded oligonucleotide" on line 10 of claim 17 is indefinite because it lacks antecedent basis in the recitation of "a plurality of double-stranded oligonucleotides."

In response, Applicants herein amend claim 17 in order to recite "one of said plurality of double-stranded oligonucleotides" on line 10. Applicants respectfully submit that this amendment is sufficient to overcome this rejection. Please see amended claim 17. Favorable reconsideration is respectfully requested.

Additionally, Applicants herein cancel without prejudice withdrawn claims 1-16 and 34-42. Applicants retain the right to file a divisional application to these claims at a later date.

Applicants' Response to Claim Rejections under 35 U.S.C. §103

Claims 17, 21, 22 24-27, 29 and 30 are rejected under 35 U.S.C. §103(a) as being unpatentable over Corn et al. (U.S. Patent No. 6,127,129) in view of Andreadis et al. (Nucleic Acids Research, vol. 28, e5, January 2000).

It is the position of the Office Action that Corn discloses the invention as claimed, with the exception of teaching "a hydrophilic repeating unit (expressed by $-(O-R_1)_n$, wherein R_1 is an alkylene group of the polymer (i.e., polyethylene glycol, or PEG)." The Office Action goes on to state that Corn teaches the base method that differs from the instantly claimed method because Corn does not teach a heterobifunctional linker wherein the X group and the Y group linked with a polyethylene glycol portion is linked to the MUAM. The Office Action relies on Andreadis to provide this teaching.

Corn is directed at a process to create biomolecule and/or cellular arrays on metal surfaces. Corn discloses a fabrication scheme for a biochip, where a PEG background surrounds a plurality of DNA attachment sites. As illustrated in Figure 4, in the DNA attachment sites,

DNA is attached to 11-mercaptoundecylamine (MUAM) on a gold (Au) substrate via sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SSMCC). In the background area, PEG is attached to MUAM on the gold substrate. SSMCC does not include a hydrophilic repeating unit expressed by $-(O-R_1)_n$, wherein R_1 is an alkylene group, with n being an integer between 4 and 450. Where the Office previously regarded MUAM as part of the linker, the pending Office Action states that "MUAM is interpreted as part of the surface to which the SSMCC linker is attached." Office Action, page 11.

Andreadis is directed at the use of immobilized PCR primers to generate covalently immobilized DNAs for in vitro transcription/translation reactions. Andreadis is directed at attachment of DNA to beads, not to a planar surface as in Corn. In Andreadis, the beads are silanized. See page ii, right column, first partial paragraph. The silanized beads are then treated with either N-succinimidyl-(4-iodoacteyl)aminobezoate (SIAB) or N-hydroxysuccinimidyl polyethyleneglycol maleimide (NHS-PEG-MAL), and DNA is then attached. The Office Action identifies NHS-PEG-MAL as a heterobifunctional crosslinker. The NHS-PEG-MAL beads are referred to as E-PEG or H-PEG. Other attachment schemes and crosslinkers are used in Andreadis. See page iii, left column, first full paragraph. PCR is then conducted on each bead. See page iii, right column, first and second full paragraphs.

In attachments schemes <u>besides</u> those involving heterobifunctional cross-linkers, PCR was conducted <u>after</u> the DNA was attached to the beads. However, referring to Chrisey et al. (reference 8), Andreadis states that "[w]e initially tested 5'-thiolated primers attached via heterobifunctional crosslinkers to amine-functionalized CPG, and, as expected (8), this chemistry

proved to be heat labile (data not shown)." Page iv, right column, first full paragraph. Andreadis also identifies H-PEG as one of "...those which underwent post-PCR immobilization onto HDA crosslinker-modified CPG." Page v, left column, first partial paragraph. Andreadis further identified H-PEG and E-PEG as "...results for amplicons produced from 5'-thiol-modified primers and subsequently attached to EDA- or HDA-modified beads." Page vi, right column, first full paragraph.

The Office Action alleges that it would have been obvious to modify Corn by replacing SSMCC with NHS-PEG-MAL from Andreadis. The Office Action alleges that one having ordinary skill in the art would have "been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing subsequent enzymatic reactions (in the form of PCR reactions) to be performed using the immobilized nucleic acids as explicitly taught by Andreadis." Office Action, page 6 (emphasis added).

However, as discussed above, Andreadis teaches away from this alleged reason to combine the reference. Andreadis teaches that DNAs attached via heterobifunctional linkers such as NHS-PEG-MAL are heat labile, and thus are not usable for PCR when immobilized on a surface. In other words, Andreadis teaches that a linker such as NHS-PEG-MAL will not survive the heat of a PCR reaction. Thus, Andreadis teaches that for a linker such as NHS-PEG-MAL, the PCR is first conducted, and then the resulting amplicons are attached to the beads via NHS-PEG-MAL. In other words, the PCR is conducted before the DNA is attached to the beads. Thus, the PCR is not a "subsequent enzymatic reaction[]." As such, Andreadis specifically

teaches away from the alleged reason for combination of references cited by the Office Action. Accordingly, the alleged reason to combine the references is not present.

Furthermore, the subsequent attachment of the amplicons to the beads with PEG after PCR is not effective, as compared to other attachment schemes. For example, see Table 2, which states that H-PEG has less specific binding of DNA (75.3±0.28 nmol DNA/g bead) than H-SIAB (154±2.5 nmol DNA/g bead) and PC-H (374±0.39 nmol DNA/g bead). Similarly, E-PEG has less specific binding of DNA (15.4±0.63 nmol DNA/g bead) than E-SIAB (77±0.75 nmol DNA/g bead) and PC-E (141±0.48 nmol DNA/g bead). In other words, PEG has the lowest amount of specific binding of DNA of all attachment schemes, both in the EDA category and the HDA category. As a result, the beads with the PEG linker cannot absorb biomolecules, because of the low quantity of bead-immobilized DNA. In view of this, one having ordinary skill in the art would not see a reason to make modify Corn by including an NHS-PEG-MAL crosslinker, as proposed by the Office Action. Thus, Applicants respectfully submit that there is no reason to combine the cited references.

Next, Applicants discuss the unexpected results shown by the previously-submitted Kyo reference. It appears that there is a question as to whether $-(CH_2)_8-$ in Kyo is part of the linker or not. It appears that $-(CH_2)_8-$ could alternatively be interpreted as a part of the surface or as a part of the linker. Regardless, Kyo was cited to show an unexpected result between the following configurations:

Surface—S—$(CH_2)_8$—NHS—PEG—MAL—DNA
Surface—S—$(CH_2)_8$—NH—SSMCC—DNA

Corn shows the following configuration:

Surface—S—$(CH_2)_{11}$—NH—SSMCC—DNA

Being that the attachment configuration of Corn is highly similar to the SSMCC attachment configuration of Kyo, and differs only in the number of repeats of the surface-bound CH_2 groups, teachings of Kyo are relevant to the pending rejection. Thus, Kyo illustrates the unexpected results of using a heterobifunctional linker of claim 1, such as NHS-PEG-MAL, as compared with using a heterobifunctional linker of Corn (SSMCC).

The Office Action discusses the scope of the unexpected results. In Kyo, only one example of a heterobifunctional linker meeting the requirements of claim 1 is represented. Claim 1 requires that the linker has two different functional groups joined by a hydrophilic repeating unit expressed by – $(O—R_1)_n$—. It appears that there are many heterobifunctional linker molecules which will meet the requirements of claim 1 besides NHS-PEG-MAL. As such, the Office Action states that "because Applicant has presented only one example having the alleged unexpected results, adequate basis for concluding that similar results would be obtained has clearly not been established." Office Action, page 12.

In other words, the Office Action appears to be of the position that the unexpected results of Kyo are not commensurate in scope with the claims because the claims encompass many different heterobifunctional linkers. Thus, in order to further illustrate the unexpected results, Applicants herewith provide further evidence to show that other heterobifunctional linkers besides NHS-PEG-MAL exhibit similar unexpected results when such a heterobifunctional linker is used. In other words, Applicants herewith provide an additional "data point" representing

another heterobifunctional linkers having a hydrophilic repeating unit expressed by – $(O—R_1)_n$. Specifically, please see note 20 on page 2162 of the attached reference by Nishimura et al. This note discloses the use of NHS-PEG_{12}-MAL (MW=875, n=12). This shows that it is not only the NHS-PEG-MAL (MW=3400, n=about 70) used in the example of the specification at paragraph [0130] that exhibits the unexpected results, but also other heterobifunctional linkers such as NHS-PEG_{12}-MAL.

Additionally, the Office Action states that the example (in Kyo, presumably) "requires other specific structural limitations not listed in the previous Office Action; namely, a PEG thiol background, and 8-AOT on the Spot Region." In other words, the Office Action appears to be of the position that the unexpected results of Kyo are not commensurate in scope with the claims because Kyo includes experimental conditions not recited in the claims. As to this point, Applicants respectfully submit that a PEG thiol background and the use of 8-AOT, or equivalents, are well known in the art, and explicit discussion of this was not needed in Kyo.

Finally, Applicants provide brief comments regarding claim 25. Claim 25 requires that the solid surface includes a thin gold layer having the general formula of X'-R-Y', where X' and Y' are functional groups and R is an organic group. The Office Action considers MUAM of Corn to meet the requirements of this general formula X'-R'-Y'. It is noted that the Office Action had previously regarded the MUAM of Corn as a part of the linker, rather than as a part of the surface. Applicants respectfully submit that claim 25 is patentable at least due to its dependency on claim 21, which Applicants submit is patentable for the reasons discussed above. Favorable reconsideration is respectfully requested.

Claims 20 and 33 were rejected under 35 U.S.C. §103(a) as being unpatentable over Corn in view of Andreadis and in further view of Noblett (U.S. Patent No. 6,362,004).

It is the position of the Office Action that the combination of Corn and Fodor, as evidenced by Sato discloses the invention as claimed, with the exception of markers on the array indicative of spots. The Office Action relies on Noblett to provide this teaching. In response, Applicants respectfully submit that claims 20 and 33 are patentable at least due to their dependency on claims 17 and 21, which Applicants submit are patentable for at least the reasons discussed above. Favorable reconsideration is respectfully requested.

Claim 31 was rejected under 35 U.S.C. §103(a) as being unpatentable over Corn in view of Andreadis and in further view of Wiegel (U.S. Patent No. 6,107,034).

It is the position of the Office Action that the combination of Corn and Fodor, as evidenced by Sato discloses the invention as claimed, with the exception of transfer factors. The Office Action relies on Wiegel to provide this teaching. In response, Applicants respectfully submit that claim 31 is patentable at least due to its dependency on claim 21, which Applicants submit is patentable for at least the reasons discussed above. Favorable reconsideration is respectfully requested.

For at least the foregoing reasons, the claimed invention distinguishes over the cited art and defines patentable subject matter. Favorable reconsideration is earnestly solicited.

Should the Examiner deem that any further action by applicants would be desirable to place the application in condition for allowance, the Examiner is encouraged to telephone applicants' undersigned attorney.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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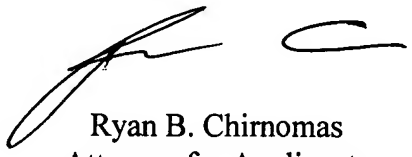

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Enclosures: Y. Nishimura, et al. "A proof of the specificity of kanamycin-ribosomal RNA interaction with designed synthetic analogs and the antibacterial activity." Bioorganic & Medical Chemistry Letters 15 (2005) 2159-2162.